```
=> d his

     (FILE 'HOME' ENTERED AT 09:07:30 ON 01 JUN 2006)

     FILE 'CAPLUS, BIOSIS, MEDLINE' ENTERED AT 09:08:07 ON 01 JUN 2006
L1        644567 S INSULIN
L2       2280313 S DERIVATIVE?
L3          9988 S L1 (L) L2
L4         66761 S LIPOPHIL?
L5            92 S L3 (L) L4
L6            51 DUP REM L5 (41 DUPLICATES REMOVED)
L7            39 S L6 AND PY<2002
L8           145 S L3 AND HEXAMER?
L9           102 DUP REM L8 (43 DUPLICATES REMOVED)
L10           71 S L9 AND PY<1998
L11           59 S L10 AND PY<1996
L12            0 S L9 AND LIPOPHILIC
L13            0 S L9 AND LIPOHIL?
L14            3 S L9 AND LIPO?
L15            0 S L5 AND HEXAMER?
L16           19 S L5 AND STAB?
L17            0 S L16 AND PROLOGN
L18            0 S L16 AND LIFE
L19            1 S L16 AND TERMIN?
                 E MARKUSSEN JAN /AU
                 E HAVELUND SVEND /AU
L20           88 S E3
                 E MARKUSSEN JAN /AU
L21          116 S E3
                 E BRANDT JAKOB /AU
L22           44 S E3
                 E HANSEN PETER /AU
                 E KURTZHALS PETER  /AU
L23           44 S E3
L24           33 S L20 (L) L21
L25            3 S L22 (L) L23
L26            3 S L24 AND L22
L27           15 S L24 AND L23
L28           10 DUP REM L27 (5 DUPLICATES REMOVED)
L29            5 S L28 AND INSULIN AND DER?

=
```

L29 ANSWER 1 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
TI **Insulin derivatives**
IN **Markussen, Jan**; Jonassen, Ib; **Havelund, Svend**; Brandt, Jakob; **Kurtzhals, Peter**; Hansen, Per Hertz; Kaarsholm, Niels Christian
PY 1996
1996
1996
2000
1998
1998
2003
1999
1999
2002
2002
2003
1997
2001
2002
2003
2004
SO PCT Int. Appl., 58 pp.
CODEN: PIXXD2
TI **Insulin derivatives**
IN **Markussen, Jan**; Jonassen, Ib; **Havelund, Svend**; Brandt, Jakob; **Kurtzhals, Peter**; Hansen, Per Hertz; Kaarsholm, Niels Christian
AB **Insulin derivs**. in which a lipophilic group having from 12 to 40 carbon atoms is attached to the α-amino group of the. . . the carboxy group of the C-terminal amino acid in the B-chain have a protected profile of action. Thus, LysB30(Nε-tetradecanoyl)ThrB29 human **insulin** was prepared via polymerase chain reaction (PCR) and reaction with tetradecanoic acid N-hydroxysuccininmide ester.
ST **insulin** tetradecanoyl prepn
IT 11061-68-0DP, Human **insulin**, **derivs**. 184181-38-2P
184181-40-6P 184181-41-7P 184181-43-9P 184181-44-0P 184181-47-3P
184181-61-1P
RL: BPN (Biosynthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of **insulin derivs**.)
IT 184181-45-1P 184181-49-5P 184181-50-8P 184181-51-9P 184181-52-0P
184181-54-2P 184181-56-4P 184181-59-7P 184181-62-2P 184181-64-4P
184246-94-4P
RL: BPN (Biosynthetic preparation); RCT (Reactant); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation of **insulin derivs**.)
IT 184181-53-1P 184181-55-3P 184181-57-5P 184181-60-0P 184181-63-3P
RL: BPN (Biosynthetic preparation); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation of **insulin derivs**.)
IT 69888-86-4 120177-51-7 184045-66-7 184045-67-8 184181-58-6
184493-04-7 184493-05-8 184493-06-9 184493-07-0 184493-08-1
184493-09-2 184493-10-5 184493-11-6 184493-12-7 184493-13-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of **insulin derivs**.)
IT 184181-46-2P 184181-48-4P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of **insulin derivs**.)

L29 ANSWER 2 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
TI Albumin Binding and Time Action of Acylated **Insulins** in Various Species
AU **Kurtzhals, Peter**; **Havelund, Svend**; Jonassen, Ib; Kiehr, Benedicte; Ribel, Ulla; **Markussen, Jan**
PY 1996
SO Journal of Pharmaceutical Sciences (1996), 85(3), 304-8

CODEN: JPMSAE; ISSN: 0022-3549

TI Albumin Binding and Time Action of Acylated **Insulins** in Various Species

AU **Kurtzhals, Peter**; **Havelund, Svend**; Jonassen, Ib; Kiehr, Benedicte; Ribel, Ulla; **Markussen, Jan**

AB **Insulins** acylated with fatty acids at the ε-amino group of NεB29 constitute a new class of **insulin** analogs, which are prolonged-acting due to albumin binding. In the present study it is shown that the affinity of fatty acid acylated **insulins** for albumin varies considerably (>50-fold) among species. The relative affinities of acylated **insulin** for albumin in human, pig, and rabbit serum are about 1:1.5:35. The severalfold higher binding affinity in rabbit serum than. . . pig serum and human serum, the pig model should provide a useful estimate of the degree of protraction of acylated **insulin** in humans. The results emphasize that species differences in ligand binding can be of major importance in the preclin. evaluation. . .

ST acylated **insulin** albumin binding

IT Rabbit
Swine
(albumin binding and time action of acylated **insulins** in various species)

IT Albumins, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(albumin binding and time action of acylated **insulins** in various species)

IT 11061-68-0D, Human **insulin**, NεB29-fatty acylated **derivs**. 169148-58-7 169148-62-3 169148-63-4
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(albumin binding and time action of acylated **insulins** in various species)

L29 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN

TI Albumin binding of **insulins** acylated with fatty acids: characterization of the ligand-protein interaction and correlation between binding affinity and timing of the **insulin** effect in vivo

AU **Kurtzhals, Peter**; **Havelund, Svend**; Jonassen, Ib; Kiehr, Benedicte; Larsen, Ulla D.; Ribel, Ulla; **Markussen, Jan**

PY 1995

SO Biochemical Journal (1995), 312(3), 725-31
CODEN: BIJOAK; ISSN: 0264-6021

TI Albumin binding of **insulins** acylated with fatty acids: characterization of the ligand-protein interaction and correlation between binding affinity and timing of the **insulin** effect in vivo

AU **Kurtzhals, Peter**; **Havelund, Svend**; Jonassen, Ib; Kiehr, Benedicte; Larsen, Ulla D.; Ribel, Ulla; **Markussen, Jan**

AB Albumin is a multifunctional transport protein that binds a wide variety of endogenous substances and drugs. **Insulins** with affinity for albumin were engineered by acylation of the ε-amino group of LysB29 with saturated fatty acids containing 10-16 carbon atoms. The association consts. for binding of the fatty acid acylated **insulins** to human albumin are in the order of 104-105 M-1. The binding apparently involves both non-polar and ionic interactions with the protein. The acylated **insulins** bind at the long-chain fatty acid binding sites, but the binding affinity is lower than that of the free fatty. . . relatively small degree on the number of carbon atoms in the fatty acid chain. Differences in affinity of the acylated **insulins** for albumin are reflected in the relative timing of the blood-glucose-lowering effect after s.c. injection into rabbits. The acylated **insulins** provide a breakthrough in the search for soluble, prolonged-action **insulin** prepns. for basal delivery of the hormone to the diabetic patient. We conclude that the biochem. concept of albumin binding can be applied to protract the effect of **insulin**, and suggest that **derivatization** with albumin-binding ligands could be generally applicable to prolong the action profile of peptide drugs.

ST albumin binding acylated **insulin** prolonged action

IT Blood sugar
(albumin binding of **insulins** acylated with fatty acids prolong blood sugar-lowering action)
IT Fatty acids, biological studies
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(albumin binding of **insulins** acylated with fatty acids prolong blood sugar-lowering action)
IT Albumins, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(albumin binding of **insulins** acylated with fatty acids prolong blood sugar-lowering action)
IT 9004-10-8D, **Insulin**, acylated with fatty acids
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(albumin binding of **insulins** acylated with fatty acids prolong blood sugar-lowering action)

L29 ANSWER 4 OF 5 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
TI **Insulin derivatives.**
AU **Markussen, Jan** [Inventor, Reprint Author]; Jonassen, Ib [Inventor]; **Havelund, Svend** [Inventor]; Brandt, Jakob [Inventor]; **Kurtzhals, Peter** [Inventor]; Hansen, Per Hertz [Inventor]; Kaarsholm, Niels Christian [Inventor]
PY 2003
SO Official Gazette of the United States Patent and Trademark Office Patents, (Sep 16 2003) Vol. 1274, No. 3. http://www.uspto.gov/web/menu/patdata.html . e-file.
ISSN: 0098-1133 (ISSN print).
TI **Insulin derivatives.**
AU **Markussen, Jan** [Inventor, Reprint Author]; Jonassen, Ib [Inventor]; **Havelund, Svend** [Inventor]; Brandt, Jakob [Inventor]; **Kurtzhals, Peter** [Inventor]; Hansen, Per Hertz [Inventor]; Kaarsholm, Niels Christian [Inventor]
AB The present invention relates to **insulin derivatives** in which a lipophilic group having from 12 to 40 carbon atoms is attached to the alpha-amino group of the. . .
IT Major Concepts
Pharmacology
IT Chemicals & Biochemicals
insulin derivatives: antidiabetic-drug, hormone-drug, metabolic-drug
RN 9004-10-8D (**insulin derivatives**)

L29 ANSWER 5 OF 5 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
TI **Insulin derivatives.**
AU **Markussen, Jan** [Inventor, Reprint author]; Jonassen, Ib [Inventor]; **Havelund, Svend** [Inventor]; Brandt, Jakob [Inventor]; **Kurtzhals, Peter** [Inventor]; Hansen, Per Hertz [Inventor]; Kaarsholm, Niels Christian [Inventor]
PY 2001
SO Official Gazette of the United States Patent and Trademark Office Patents, (June 26, 2001) Vol. 1247, No. 4. e-file.
CODEN: OGUPE7. ISSN: 0098-1133.
TI **Insulin derivatives.**
AU **Markussen, Jan** [Inventor, Reprint author]; Jonassen, Ib [Inventor]; **Havelund, Svend** [Inventor]; Brandt, Jakob [Inventor]; **Kurtzhals, Peter** [Inventor]; Hansen, Per Hertz [Inventor]; Kaarsholm, Niels Christian [Inventor]
AB The present invention relates to **insulin derivatives** in which a lipophilic group having from 12 to 40 carbon atoms is attached to the alpha-amino group of the. . .
IT Major Concepts
Pharmacology
IT Chemicals & Biochemicals
insulin derivatives: hormone-drug

L19 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN
TI Trials of lipid modification of peptide hormones for intestinal delivery
AU Muranishi, Shozo; Murakami, Masahiro; Hashidzume, Minoru; Yamada, Keigo; Tajima, Shigeru; Kiso, Yoshiaki
PY 1992
SO Journal of Controlled Release (1992), 19(1-3), 179-88
CODEN: JCREEC; ISSN: 0168-3659
AB . . . study the intestinal delivery of peptide, three typical peptide hormones with different mol. wts., TSH-releasing hormone (TRH), tetragastrin (TG) and **insulin**, were used. With the aim of increasing peptide **lipophilicity**, these peptides were chemical modified by attaching fatty acid moieties (acyl chains) to their amino **termini**; this was achieved without marked loss of pharmacol. activities. By reverse-phase HPLC, the synthesized peptide analogs, lauroyl-TRH, caproyl- and lauroyl-TG, and B1-monopalmitoyl- and B1, B29-dipalmitoyl-**insulin**, were confirmed to be more **lipophilic** than their parent peptides. These analogs retained more than 64% of the pharmacol. activities of the parent peptides, as assessed following i.v. injection in rats. The results obtained showed that the **lipophilic derivs**. were more suitable for intestinal absorption than the parent peptides and that the **stabilities** of some **derivs**. against intestinal enzymic degradation were improved. These findings suggest that, by appropriate lipid modification of the amino-**terminus** of peptides, it may be feasible to improve their intestinal delivery characteristics and their protective capabilities against enzymic degradation

L14 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2006 ACS on STN
TI Soluble, prolonged-acting **insulin derivatives**. II. Degree of protraction and crystallizability of **insulins** substituted in positions A17, B8, B13, B27 and B30
AU Markussen, J.; Diers, I.; Engesgaard, A.; Hansen, M. T.; Hougaard, P.; Langkjaer, L.; Norris, K.; Ribel, U.; Soerensen, A. R.; et al.
PY 1987
SO Protein Engineering (1987), 1(3), 215-23
CODEN: PRENE9; ISSN: 0269-2139
TI Soluble, prolonged-acting **insulin derivatives**. II. Degree of protraction and crystallizability of **insulins** substituted in positions A17, B8, B13, B27 and B30
AB . . . by B27 lysine or arginine substitutions and by B13 glutamine. The B27 residue is located on the surface of the **hexamer**, so a basic residue in this position presumably promotes the packing of **hexamers** at neutral pH. The B13 residues cluster in the center of the **hexamer**. When the electrostatic repulsive forces from 6 glutamic acid residues are abolished by substitution with glutamine, a stabilization of the **hexamer** can be envisaged. The biol. potency of insulins was measured in the free fat cell assay and in the mouse. . .
ST mutagenesis gene **insulin deriv** prepn; **insulin deriv** structure activity; crystal structure **insulin deriv**
IT Chains, chemical
(helical conformation of, of **insulin derivs**.)
IT Blood sugar
(**insulin derivs**. effect on, mol. structure in relation to)
IT Lipids, biological studies
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(metabolism of, by adipocyte, **insulin derivs**. effect on, mol. structure in relation to)
IT Bond angle
Conformation and Conformers
Crystal structure
(of **insulin derivs**.)
IT Adipose tissue, metabolism
(adipocyte, lipid metabolism by, **insulin derivs**. effect on, mol. structure in relation to)
IT Molecular structure-property relationship
(crystallization, of **insulin derivs**.)
IT Molecular structure-property relationship
(hydrophobicity, of **insulin derivs**.)
IT Molecular structure-biological activity relationship
(hypoglycemic, of **insulin derivs**.)
IT Molecular structure-biological activity relationship
(**lipogenic**, of **insulin derivs**.)
IT 9004-10-8DP, **Insulin**, **derivs**. 110068-59-2P 110068-60-5P 110068-61-6P 110068-62-7P 110068-64-9P 110068-67-2P 110068-70-7P 110068-71-8P 110068-72-9P 110068-73-0P 111775-84-9P 111775-85-0P 111775-86-1P 111775-87-2P 111775-88-3P 111775-89-4P 111775-90-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and biol. activity of, mol. structure in relation to)

L14 ANSWER 2 OF 3 MEDLINE on STN
TI Long-term comparison of human insulin analogue B10Asp and soluble human insulin in IDDM patients on a basal/bolus insulin regimen.
AU Nielsen F S; Jorgensen L N; Ipsen M; Voldsgaard A I; Parving H H
PY 1995
SO Diabetologia, (1995 May) Vol. 38, No. 5, pp. 592-8.
Journal code: 0006777. ISSN: 0012-186X.
AB . . . compared to soluble human insulin. The human insulin analogue B10Asp (mono/dimeric) is absorbed twice as fast as soluble human insulin (

hexameric). A double blind, randomised crossover study with a 1-month run-in period and two 2-month treatment periods was performed in 21. . .

CT . . .
drug therapy
Double-Blind Method
Drug Administration Schedule
Hemoglobin A, Glycosylated: AN, analysis
Humans
Injections, Intravenous
Insulin: AD, administration & dosage
***Insulin: AA, analogs & derivatives**
*Insulin: TU, therapeutic use
Lipoproteins, HDL Cholesterol: BL, blood
Lipoproteins, LDL Cholesterol: BL, blood
Recombinant Proteins: AD, administration & dosage
Recombinant Proteins: TU, therapeutic use
Time Factors
Triglycerides: BL,. . .

CN 0 (Blood Glucose); 0 (Hemoglobin A, Glycosylated); 0 (**Lipoproteins**, HDL Cholesterol); 0 (**Lipoproteins**, LDL Cholesterol); 0 (Recombinant Proteins); 0 (Triglycerides); 0 (insulin, Asp(B10)-)

L14 ANSWER 3 OF 3 MEDLINE on STN
TI Semisynthetic des-(B27-B30)-insulins with modified B26-tyrosine.
AU Lenz V; Gattner H G; Sievert D; Wollmer A; Engels M; Hocker H
PY 1991
SO Biological chemistry Hoppe-Seyler, (1991 Jul) Vol. 372, No. 7, pp. 495-504.
Journal code: 8503054. ISSN: 0177-3593.

AB . . . formal transpeptidation product at ArgB22--was formed in one step. Biological in vitro properties (binding to cultured human IM-9 lymphocytes, relative **lipogenic** potency in isolated rat adipocytes) of all semisynthetic analogues are reported, ranging from slightly decreased to two-fold receptor affinity and. . . typical of native insulin can be observed, and the CD-spectral effects in the near UV spectrum related to association and **hexamerization** of the native hormone are qualitatively reestablished. The results of this investigation underline the importance of position B26 to the. . .

CT Amino Acid Sequence
Circular Dichroism
Humans
***Insulin: AA, analogs & derivatives**
Insulin: BI, biosynthesis
Molecular Sequence Data
Peptide Biosynthesis
*Peptide Fragments: BI, biosynthesis
Research Support, Non-U.S. Gov't

EAST Search History

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	30801	insulin and derivativ?	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:36
L2	3754	hexamer?	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:36
L3	0	hexamer*	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:36
L4	29	hexamer???	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:36
L5	968	hexamer??	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:36
L6	840	l1 and l2	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:37
L7	108	l6 and @py<"2000"	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:37
L8	49	l6 and @py<"1998"	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:37
L9	0	l8 and stab?	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:37
L10	19	l8 and life	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:38
L11	43	l8 and composition	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:38
L12	29	l11 and stable	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:39
L13	0	l7 and lipo?	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:39
L14	19	l7 and lipophilic	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:39
L15	19	l14 and @py<"2000"	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:40

EAST Search History

L16	17	l15 and stable	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:43
L17	25	markussen adj jan	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:43
L18	32	havelund near svend	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:44
L19	8	brandt near jakob	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:44
L20	7	kurtzhals near peter	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:45
L21	50	l17 or l18 or l19 or l20	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:45
L22	50	l21 and insulin	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:45
L23	36	l22 and derivative?	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:46
L24	13	l23 and hexameric	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:46
L25	0	l24 and lipo	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:46
L26	0	l24 and lipo*	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:46
L27	0	l24 and lipo?	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:46
L28	13	l24 and lipophilic	US-PGPUB; USPAT; DERWENT	OR	ON	2006/06/01 09:47